

BIOMARKERS IN ACUTE STROKE PREDICTION

In the modern world one of the leading causes of mortality among people is stroke. Particularly, in the first thirty days after stroke the frequency of the fatality is very high, getting to 50%. Only twenty percent completely recover after stroke, while the remaining 80% stay disabled. Among questions about prophylaxis, treatment and the rehabilitation, the forecasting of acute stroke is still relevant. Despite a large number of studies performed in this area the problem of the forecasting stroke is still relevant.

In the last ten years the forecasting value of some biomarkers was studied in great details. Updates on biomarkers correlated with the risk of stroke and can be used in the forecasting models in the perspectives. The data is not always available for specialists due to the fragmentation. Therefore, this research was undertaken to analyze collected findings for last ten years about biomarkers for the forecasting acute stroke.

Keywords: acute stroke, forecasting, biomarkers.

Introduction

Acute stroke is one of the most critical medical and social problem in the world that relates to a high level of mortality and disability [1, 2]. To exemplify, six million people die per year due to acute disorders of cerebral circulation [3].

The average frequency of death in the first 30 days after a stroke varies between 17% and 34%. During the first year after stroke 50% of patients die, i.e. every second patient [2]. In 2009, Johnston and colleagues conducted a review, which analyzed mortality associated with stroke in 192 countries. Russia is in the first place according to terms of mortality from stroke from 192 studied countries (251 events per 100 thousand of population). Such developed countries as Australia, the USA, Canada, Switzerland, occupy one of the last places (184th, 186th, 189th and 191st places respectively). In the US and the UK, stroke is the third leading cause of death, affecting 750,000 people annually, 30% of which die within the first year [3,4].

In Kazakhstan more than 32,000 people suffer from stroke each year [5]. The incidence of stroke in different regions of Kazakhstan is 2.5 - 3.7 cases per 1,000 people, the mortality rate from 1.0 to 1.8 cases per 1,000 per year. About 300,000 citizens of Kazakhstan become disabled annually and their number is increased by 50 thousand a year [5].

Acute stroke is a leading cause of disability [6]. The vast majority of the stroke effect is the development of motor disorders - more 75% and cognitive impairment - 30-80% [7,8]. Studying the dynamic of incidence in the last decades shows the existence of a stable 0.5-1% trend towards growth each year [9]. Constant increase of stroke occurrence correlates with prolonged life duration and associated with this gerontological pathology. Not the last place takes the changed lifestyle and risk factors, such as physical inactivity, obesity and psychological intense [8].

Preventing disability and holding the adequate rehabilitation measures is necessary to use all instruments forecast the development of acute stroke [10]. In fact, timely correct preventive treatment in order to avoid the development of acute stroke and increasing the neurological deficit [11, 12]. The simplest and more available way of the forecasting the development acute stroke is forecasting models and usage of early detected markers [12, 13].

In the last ten years some diagnostic scales and prognostic models were developed, which forecasting a patient's risk to stroke [14, 15]. Some researchers offer to focus on new biomarkers for identified the diagnose "stroke" [16].

The **aim** of this manuscript is to analyze the biomarkers, which forecast the developing of acute stroke in patients.

This research contained publications for the last ten years, describing biomarkers, which forecast the risk of the development acute stroke in patients [17,18,19,20]. Despite of a big quantity of researches in this sphere the problem of forecasting stroke is actual so far. In the last ten years the prognostic value of some scales were deeply studied, the new data about biomarkers was received. The information is not always available for doctors and researches because of the fragmentation of data thus this research was made for the analyze and the collection data about methods of forecasting stroke in the last ten years.

The writing of this research was made as required by the prisma statement. The research was conducted in the bases data NCBI. Following key words and their combinations were required: "biomarkers AND stroke". 378 articles were identified among these articles, 28 were included in research.

Results and discussion.

According to the study, researchers often use biomarkers for the prediction of acute stroke, whereby a lot of markers are started to use in routine clinic survey. Biomarkers according to [13] - are any measured physiologic value or substance, forecasting manifestation or outcome of pathology. Following types of markers are associated with a stroke: physiologic, markers are based on methods of visualization, electrophysiological, histological, genetic and neuronal.

Physiologic markers include arterial pressure, body temperature and etc [21].

Methods of neurovisualization (computed tomography, magnetic resonance imaging) use in diagnosing of acute stroke and forecasting the possible outcome which depends on volume and the location of brain damage [22, 23, 24].

Electrocardiologic methods are related to electrophysiological, allowing to define the possibility of appearing of cardiogenic stroke. There are works which are devoted to adverse outcome of P waves observed on ECG.

Such pathology as vasculitis can be an etiologic factor of stroke and able to be used as histological marker.

Genetic researches are used widely and allow to find out individual predisposition to cardiovascular pathology and to determine its trend [25].

Serum biomarkers are becoming widely used because of available material and a high diagnostic value. Their determination became necessary manipulation for diagnostic stroke after the manifestation of event. Following serum biomarkers are used for diagnosis "stroke" and forecasting its outcome: markers of inflammatory cascade, hemostatic factors, specific markers for glial cells and neurons [13, 14, 15].

We paid much attention to this subject in the article [2], so there is no need to repeat information in this review.

For instance, the observation [26] showed the importance of measurement of evening and morning arterial pressure (AP). Regression model of Cox proved that evening and morning AP equally predict future risk of stroke. The risk of morning hypertension was more determined in subjects, who accepted antihypertensive preparations (RH: 3,55; 95% CI: 1,70 to 7,38). However, the risk of hypertension in evening time (morningBP<135/85 mmHg and eveningBP>or = 135/85 mmHg) was higher in normotension, these differences were not meaningful. In conclusion morning hypertension is a good predictor of stroke, especially among people who use the antihypertensive preparations.

The authors in the work Teemu Vepsäläinen [27] offer to use the P wave duration on ECG like a marker of atrium's conductivity disorder. This could lead to acute stroke. The forecasting meaning of the P wave duration among average age of patients was written in the article. The assessment of the relationship between the P wave duration and mortality from stroke was identified by the model of proportional risks of Cox.

Kohsaka S. and co-authors [28] assist the connection between ECG of left atrium and an ischemic stroke to ensure that the additional forecasting information on patients. The risk of the appearance an ischemic stroke correlated with the P wave duration >120 msec.

Carotid stenosis is an important factor for the ischemic stroke attack. In the work [29] different methods of visualization for diagnosis carotid stenosis is conceived in terms of prognostic criterion. The predictive potential increased slightly when two independent measurements of stenosis were used.

The patients with a second type of diabetes mellitus have been participating for 48 months in perspective observation case-control [30]. Their risk was assisted: cardiovascular death, an acute coronary syndrome, a revascularization and a stroke. The potential factors of acute stroke were identified. The prognostic models were created which were based on clinic symptoms, the computed tomography data and the level of calcination. Computed tomography and determination of the degree of calcification demonstrated an important predictive data. In conclusion computed tomography can help to predict acute stroke and a stroke, improve their outcomes computed tomography [30,31].

In an article [32] authors assist the prognostic possibility of B-type (BNP) peptide-type in developing acute stroke. The addition of BNP to CHADS2 scale improved the model. The authors came to conclusion that plasma BNP is a valuable biomarker and can be used independently and together with an established scoring system for assessing the risk of stroke, heart failure and acute coronary syndrome.

One of the most important factors of acute stroke is high cholesterol level. In observation of Framingham Offspring Study [33] information of factors which influence on a level of cholesterol in plasma and their meaning in forecasting following acute stroke was checked. The researchers assisted a relationship between markers of absorption of cholesterol, its synthesis and a 10-years risk of acute stroke. The primary endpoint was cardiac ischemia (coronary death and myocardial infarction) and the secondary endpoint was stroke, coronary insufficiency, angina pectoris, diseases of peripheral arteries, congestive heart failure. Significant differences in sex, age, body mass index, blood pressure and smoking status were observed in the analysis. In both men and women, the minimum absorption of cholesterol was associated with high triglyceride levels and reduced high-density lipoprotein (HDL), while reduced cholesterol synthesis was associated with a higher concentration of low-density lipoprotein (LDL). The Cox proportional hazards model, adjusted for standard acute stroke risk factors, showed that in women, squalene concentrations were associated with a lower risk of acute stroke than men who had squalene concentrations associated with a higher acute stroke risk. Cholesterol absorption markers did not predict acute stroke by a woman or a man. These facts show the significant sex differences in the predictive value of cholesterol synthesis markers in acute stroke [33].

Also the role of protein carrying fatty acids 4 was studied in the pathogenesis of atherosclerosis and as a predictor of stroke. Protein carrying fatty acids 4 (FABP4) plays an important role in the absorption of cholesterol by macrophages and the associated inflammation. To further works was studied the role of FABP4 in human atherogenesis, the regulation of FABP4 in patients with atherosclerosis of carotid arteries and ischemic stroke [34].

The levels of FABP4 were determined in plasma by patients with asymptomatic (n = 28) and symptomatic (n = 31) atherosclerosis of carotid arteries and by 202 patients with acute ischemic stroke. The levels of FABP4 were higher by patients with atherosclerosis of carotid arteries both systemically and by atherosclerotic lesions, with specific levels of mRNA. Immunostaining of carotid plaques showed localization of FABP4 on macrophages. Activated platelets and oxidized LDL were strong incentives for FABP4. By measuring FABP4 at the time of acute ischemic stroke were determined its high levels in plasma [34].

The concentration of FABP4 is associated with atherogenesis, plaque instability and adverse outcome by patients with atherosclerosis of carotid arteries and acute ischemic stroke.

The research was made [35] for predicting recurrent stroke in a cohort of 5,575 patients with an ischemic stroke. Relapse was observed in 221 during the following year. Estimates of the Kaplan-Meier cumulative frequency of recurrent stroke were 2.5%, 3.6% and 4.8% at 3, 6 and 12 months, respectively. The subsequent stroke or death for SPI-II in low-, medium- and high-risk groups was 8.2%, 24.5%, 35.6%, respectively (trend, P = 0.001). The C-statistics for SPI-II were 0.62 (95% CI, 0.61-0.64). SPI-II was recognized as a marginally effective tool in identifying patients with recurrent ischemic stroke. "A simple adaptation method improved the interpretability of prediction models for composite end point" authors proposed alternative variants of adaptation of prognostic models to clinical and diagnostic use [36].

In the article [37] are presented facts of the genetic basis of ischemic strokes. Single nucleotide polymorphisms (SNPs) were identified as associated with ischemic stroke. However, a multidimensional approach is needed to develop a prognostic model of ischemic stroke as a complex phenotype. The ability to predict using SNPs allows doctors to identify people who have high possibility to develop a phenotype, including genetic risk factors in the model [37]. The first intelligent genomic model of ischemic stroke was demonstrated and used gene data that affect the risk of stroke. From a clinical perspective, these biomarkers will prove particularly useful for predicting cardioembolic strokes.

For the last 2-3 years NCBI shows a lot of data concerning genes predisposing acute stroke occurrence. This area of research is very wide and difficult in practical usage, however quiet promising. Because acute stroke is a multifactorial pathology amount of genes should be observed for prediction of stroke getting to hundreds. But of course there are genetic markers, which are given high expectations.

CETP gene is determined as responsible for synthesis of cholesteryl ester transfer protein (CETP). Blockade of CETP is a potentially important strategy for prevention and treatment of cardiovascular disease, including stroke [39]. Authors mention that early determination of CETP gene would help to predict and predispose acute stroke [39].

Polymorphism in genes 9p21/CDKN2, EDNRA and SOX17 which are involved in vessel wall remodeling could predict occurrence of stroke or cerebral aneurysms [40]. However multiple factors contribute to aneurysm formation and acute stroke and the contributions of blood flow dynamics and risk factors as age, hypertension, smoking, and alcohol usage, cannot be ignored. While these elements are important to development and manifestation of acute stroke, genetic influence may predispose certain patients to formation of it [40].

MicroRNAs are endogenously expressed RNA molecules that function to inhibit mRNA translation and have key roles in the pathophysiological processes of stroke development. Several microRNAs, and their target genes, are recognized to be involved in include promoting angiogenesis, neurogenesis and neuroprotection and repair mechanisms [41]. So microRNAs are studying not only as pathophysiological member, but also as a recovery therapy target in acute stroke.

The most novel and promising direction of prediction of cardiovascular diseases is microbiota influencing. A lot of information published concerning TMAO production, microbiota-induced neuroinflammation and increased sympathetic activity [42].

These factors trigger the atherosclerosis formation and arterial hypertension occurrence, which are known as leading risk factors of stroke manifestation [43].

Conclusion.

Conducted analysis of biomarkers forecasting the development of acute stroke made it possible to conclude that this direction is promising. Creation of combinatorial prognostic models of acute stroke occurrence is particularly relevant, based on the combination of several biomarkers and the possibilities of mathematical modeling. Determination of genetic markers is a very relevant direction; however applying of these markers in practical healthcare is still problematic. Development of multimarker panels including genetic markers with a high level of evidence would solve question of early acute stroke prediction.

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БИОМАРКЕРЛЕРДІҢ БІРІКТІРІЛГЕН БОЛЖАУ ЖІТІ ИНСУЛЬТ

Түйін: Қазіргі заманда өлім-жітілік пен мүгедектік себептерінің ішінде жетекші орынды инсульт алады. Инсульттен кейін алғашқы отыз күнде өлімге әкелудің орташа жиілігі 50%-ға дейін ауытқып тұрады. Инсультпен ауырған науқастардың тек жиырма процент ғана барлық функциялары қалпына келеді, ал қалған жетпіс процент өмір бойы мүгедек болып қалады. Мәселелерімен қатар, алдын алу, емдеу және оңалту инсульт, өзекті мәселе болып табылады, оны болжау. Саны көп екеніне қарамастан, жүргізілген зерттеулер осы саладағы проблема болжау инсульт әлі күнге дейін өзекті күйінде қалып отыр.

Соңғы 10 жылда кей шкалалардың болжамдық құндылықтары терең зерттелді. Биомаркерлер туралы жаңа мәліметтер алынды, қанда олардың пайда болуы инсульттің пайда болу қаупін корреляциялайды және болашақта болжау үлгілері ретінде қолданылуы мүмкін. Ақпаратты алу шашыраңқылықтың кедергілердің болуына байланысты специалисттер үшін қиындықтар тудырады. Соңдықтан бұл жүйелік шолу талдау және соңғы оң жылда инсульттің нәтижесін болжау әдістері туралы бар мәліметтерді біріктіру мақсатында жүргізілді.

Түйінді сөздер: ми инсульты, болжау, биомаркерлер.

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БИОМАРКЕРЫ В ПРОГНОЗИРОВАНИИ ОСТРОГО ИНСУЛЬТА

Резюме: На данный момент одно из ведущих мест среди причин смертности населения принадлежит инсультам. Средняя частота летального исхода в течение первых тридцати дней после инсульта очень высока, достигая 50 %. Только у 20 % перенесших инсульт полностью восстанавливаются все функции, в то время как 80% из данных пациентов, навсегда остаются инвалидами. Наряду с вопросами профилактики, лечения и реабилитации инсульта, актуальным является вопрос его прогнозирования. Несмотря на большое количество проведенных исследований в этой области проблема прогнозирования инсульта до сих пор остается актуальной.

Прогностическая ценность некоторых биомаркеров была изучена за последние десять лет. Появились сведения о биомаркерах, появление которых в крови коррелирует с риском инсульта, и которые в перспективе могут использоваться в прогностических моделях. Информация не всегда доступна для специалистов в силу своей разрозненности. Данное исследование было проведено, чтобы проанализировать имеющиеся сведения о биомаркерах за последние десять лет, способных предсказать развитие инсульта.

Ключевые слова: мозговой инсульт, прогнозирование, биомаркеры.